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Dose-Dependent Pharmacokinetics of Mezlocillin in Relation to Renal Impairment

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The dose dependence of mezlocillin pharmacokinetics was examined in relation to renal function after intravenous doses of 1 and 5 g in 16 subjects with various degrees of renal impairment. Dose and time-average model-independent physiological parameters were calculated from plasma concentration and urinary excretion data. Lack of superimposition of plasma concentration profiles occurred between dosage levels with a twofold exaggeration of areas under the curve produced between doses of 1 and 5 g. Decreased plasma clearances at the higher dose were caused partly by nonlinear renal clearance, but more markedly by dose dependence in nonrenal clearances. At each dosage level, these parameters were examined in relation to creatinine clearances. Plasma and renal clearances exhibited a typical linear correlation with creatinine clearance for each dose level. However, nonrenal clearances demonstrated a linear relationship with creatinine clearance at the 1-g dose, but apparent saturation of this pathway produced lower and relatively constant nonrenal clearance values at the 5-g dose. Mezlocillin pharmacokinetics are thus influenced by both dose and renal function over the dosage range of 1 to 5 g. Saturation in renal clearance and probably in biliary clearance explains the unusual disposition characteristics of mezlocillin observed in this and previously reported studies.

Mezlocillin is a semisynthetic ureidopenicillin with pharmacokinetic properties similar to those of other penicillins in that it exhibits a small volume of distribution and undergoes a mixed degree of renal and nonrenal elimination. However, the drug appears unusual in that its disposition is markedly nonlinear. Bergan (4) observed a decrease in renal clearance (Cl_R) from 19 to 13 liters per h over a 1- to 5-g dosage range of mezlocillin given to normal volunteers. The fall in nonrenal clearance (Cl_{NR}) was even greater as values of 12 and 4 liters per h were observed at these dosage extremes. The secondary clearance mechanism involves an appreciable degree of biliary excretion of the drug (6), which is decreased in the presence of probenecid (20).

The implications of these processes in patients with renal impairment have not been fully explored. Although several studies of mezlocillin disposition in uremic patients have been carried out (5, 9, 12, 13), none has involved crossover evaluation of low and high dosages of the drug in the pharmacokinetic elaboration of the data in patients with various degrees of renal impairment. This was the purpose of our investigation.

MATERIALS AND METHODS

Subjects. Sixteen ambulatory adult volunteers who gave informed consent for the study were initially separated into three groups based on renal function (Table 1). Females of childbearing age, persons with a history of hypersensitivity to penicillins or cephalosporins, and subjects with major cardiovascular or hepatobiliary disorders or fluctuating renal function were excluded. The participants received no other antibiotics during the study. Creatinine clearances (Cl_{CR}) were determined over 24 h within 4 days of each patient study. Complete blood counts, blood chemistries, and urinalyses were performed before and after each dose. All subjects were monitored closely for signs of hypersensitivity or other adverse reactions.

Each subject was studied in a randomized crossover fashion, receiving both a 1- and 5-g dose, with at least 4 days elapsing between doses. The protocol was approved by both hospital and university human research committees.

Drug. Mezlocillin, provided by Miles Pharmaceuticals (batch no. 10523-34), was administered as the sodium salt. The 1- and 5-g doses were dissolved in 10 and 50 ml of sterile water. Each dose was administered over a 5-min infusion period into a forearm vein.

Samples. Venous blood was obtained from an arm contralateral to drug administration. Samples were taken before drug infusion and at 5, 15, 30, 45, 60, and

TABLE 1. Characteristics of the subjects

Subject no.	Sex	Age (yr)	Height (cm)	Weight (kg)	Body surface area (m^2)	Diagnosis	Cl_{CR} (liters h^{-1} 1.73 m^{-2} with dose of (g):	
							1	5
1	M	28	190	90.7	2.19	Normal	5.52	5.52
2	M	25	180	79.4	1.99	Normal	6.97	6.97
3	M	23	183	83.9	2.06	Normal	6.02	6.02
4	M	24	186	79.8	2.04	Normal	6.51	6.51
5	M	22	182	86.6	2.08	Normal	9.86	9.86
6	M	25	176	65.3	1.80	Normal	4.51	4.51
7	M	51	188	90.8	2.17	Polycystic kidney	0.84	1.05
8	F	56	158	41.9	1.36	Polycystic kidney	1.05	0.47
9	F	63	160	102.2	2.03	Analgesic overdose	2.56	3.12
10	F	65	147	61.3	1.54	Diabetes mellitus	0.44	0.77
11	M	49	178	86.7	2.05	Wegners granulomatosis	3.09	3.05
12	M	55	178	110.3	2.26	Focal segmental glomerulosclerosis	1.73	1.82
13	M	70	178	71.3	1.87	Artereolar nephrosclerosis	1.60	1.32
14	M	58	176	79.5	1.96	Polycystic kidney	2.40	2.27
15	M	65	178	78.1	1.96	Artereolar nephrosclerosis	1.87	2.28
16	M	46	180	97.2	2.17	Renal vascular stenosis	2.33	2.36

90 min and 2, 3, 4, and 8 h after infusion from subjects with Cl_{CR} >3.6 liters per h. Additional samples were taken at 5, 6, 7, 12, and 24 h from subjects with Cl_{CR} <3.6 liters per h. All blood was taken via a heparin trap except the 24-h samples. The heparin solution was drained from the tubing before the collection of blood. Blood samples were centrifuged, and the serum was separated within 30 min and frozen at −20°C until assayed. Studies in our laboratory demonstrated mezlocillin stability in serum and urine frozen at −20°C for at least 2 months.

Urine samples were obtained before drug infusion (to ensure absence of drug) and at 0 to 1, 1 to 3, 3 to 5, 5 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 h from subjects with Cl_{CR} <3.6 liters per h. Urine volumes were measured, and samples were frozen at −20°C until assayed.

Assays. Cl_{CR} were determined by an SMAC Autoanalyzer (Technicon) in the hospital pathology laboratory. Mezlocillin concentrations in serum and urine were measured with an agar-well diffusion assay (3). The medium was 1.5% nutrient agar (Difco Laboratories), and the bioassay organism was a spore suspension of *Bacillus subtilis* (Difco; ATCC 6633). Mezlocillin standards ranging from 80 to 0.625 μg/ml were prepared in human serum and urine. Patient samples with concentrations greater than 80 μg/ml were diluted with serum or urine appropriately. Plates were incubated at 37°C for 12 h, and triplicate zone diameters were measured on an antibiotic zone reader. The within-day coefficients of variation were 3.1 and 2.6% for the low and high assay extremes, whereas the between-day coefficients of variation were 8.0 and 9.5%, respectively.

Pharmacokinetics. The disposition of mezlocillin was described initially in terms of the SHAM (slope, height, area, moment) properties of the curves (10). This approach is gaining increased use in pharmacokinetics as it permits calculation of the essential parameters of interest without the need to cast the equations in the complex forms which reflect specific compartmental models. This both simplifies and makes more uniform the data-fitting process and allows the equations to be described more compactly for any number of exponential terms (10). Plasma concentrations (C_p) as a function of time (t) were fitted by NONLIN least-squares regression (15) to the function:

$$C_p = \sum_{i=1}^{n} C_i e^{-\lambda_i T} (e^{\lambda_i T} - 1)/\lambda_i T \quad (1)$$

where λ_i's are slope values, C_i's are ordinate intercepts, and T is the 5-min infusion interval (21). Reciprocal C_p values were found to be acceptable as weighting factors for generating a normal distribution of weighted residuals in NONLIN. The area (AUC) was calculated from:

$$AUC = \sum_{i=1}^{n} C_i/\lambda_i \quad (2)$$

and the first moment (AUTC) was calculated from:

$$AUTC = \sum_{i=1}^{n} C_i/\lambda_i^2 \quad (3)$$

Assuming a common mammillary model with clear-

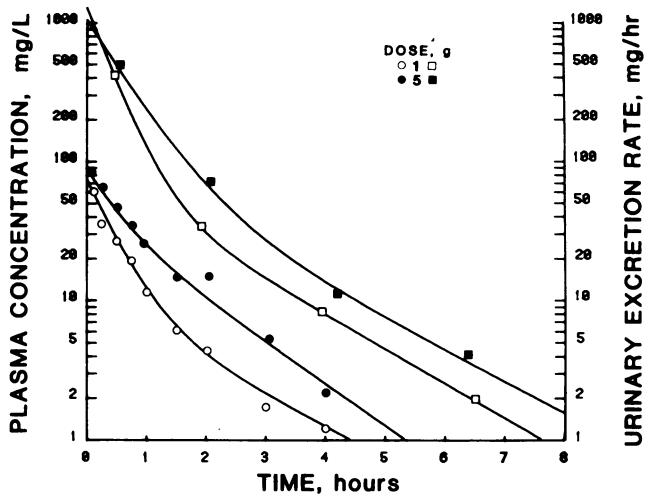

FIG. 1. Plasma concentrations (circles) and urinary excretion rates (squares) of mezlocillin after 1- (open symbols) and 5-g (solid symbols) doses in a subject with normal renal function (Cl_{CR} = 6.02 liters h^{-1} 1.73 m^{-2}). The actual data for the 5-g dose were normalized (divided by 5) to depict dose dependence. Symbols are experimental data, and curves are least-square lines fitted by a biexponential equation (equation 1).

ance from the central compartment, the following dose and time-average pharmacokinetic parameters were calculated from the dose (D_0) and SHAM properties (10):

$$V_c = D_0/\sum_{i=1}^{n} C_i \quad (4)$$

where V_c is the volume of the central compartment;

$$Cl_p = D_0/AUC \quad (5)$$

where Cl_p is plasma clearance;

$$V_{ss} = Cl_p \cdot AUTC/AUC \quad (6)$$

where V_{ss} is the steady-state volume of distribution. Similarly, the mean Cl_R was obtained from the total urinary recovery ($A\bar{u}$):

$$Cl_R = A\bar{u}/AUC \quad (7)$$

The Cl_{NR} was calculated by difference:

$$Cl_{NR} = Cl_p - Cl_R \quad (8)$$

All but one C_p-versus-t curve was biexponential; the values of V_c could not be generated for the monoexponential curve.

Clearance data were normalized for body surface area (1.73 m^2), whereas distribution volumes are expressed as distribution coefficients (liters per kilogram) (10).

Statistics. Regression analyses usually involved use of the weighted perpendicular least-squares method for fitting data where both values are subject to error (17). The paired t-test was employed for the examination of crossover pharmacokinetic parameters (18).

RESULTS

Disposition pattern. The plasma concentrations and excretion rates of 1- and 5-g (normalized to 1 g by dividing by 5) doses of mezlocillin are shown for a subject with normal renal function (Fig. 1) and for a subject with impaired renal function (Fig. 2). Both figures illustrate the typical biexponential pattern and lack of superimposition of the normalized data. The AUC values for the 5-g dose, when normalized (divided by 5) were 2.00 ± 0.44 times greater than that of the 1-g dose at all levels of renal function. These differences were statistically significant (t = 4.97, $P < 0.001$).

Elimination clearances. The Cl_p of mezlocillin obtained after 1- and 5-g doses are shown in relation to Cl_{CR} in Fig. 3. In this and subsequent graphs, crossover data can be evaluated by vertical assessment of patients at a specific Cl_{CR}. However, small differences in Cl_{CR} sometimes were found between studies in individual patients (Table 1).

To evaluate the dual effects of dose and renal function, the experimental data are usually shown in the form of regression plots. This also obviates the need for arbitrary splitting of patients into subgroups based on Cl_{CR} clusters.

The Cl_p values obtained after 1-g doses of mezlocillin were appreciably greater than those after the 5-g dosage (t = 7.97, $P < 0.001$). The data show a strong linear correlation between Cl_p and Cl_{CR}. The regression coefficients of this and subsequent figures are given in the legend where appropriate.

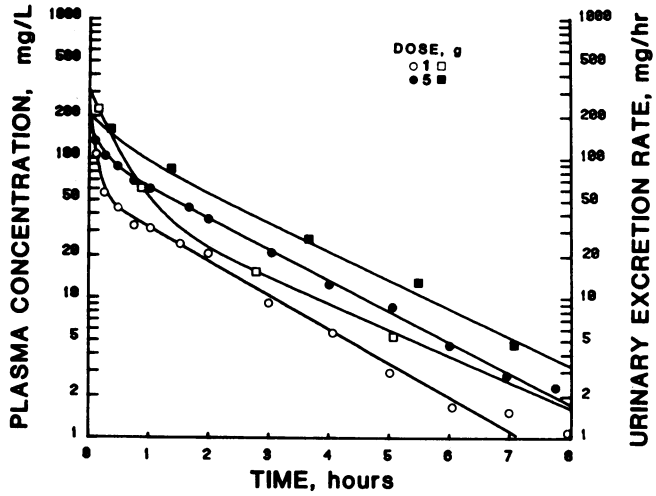

FIG. 2. Plasma concentrations and urinary excretion rates of mezlocillin in a patient with renal impairment (Cl_{CR} = 2.78 liters h^{-1} 1.73 m^{-2}). Symbols, normalization, and curves are defined as in the legend to Fig. 1.

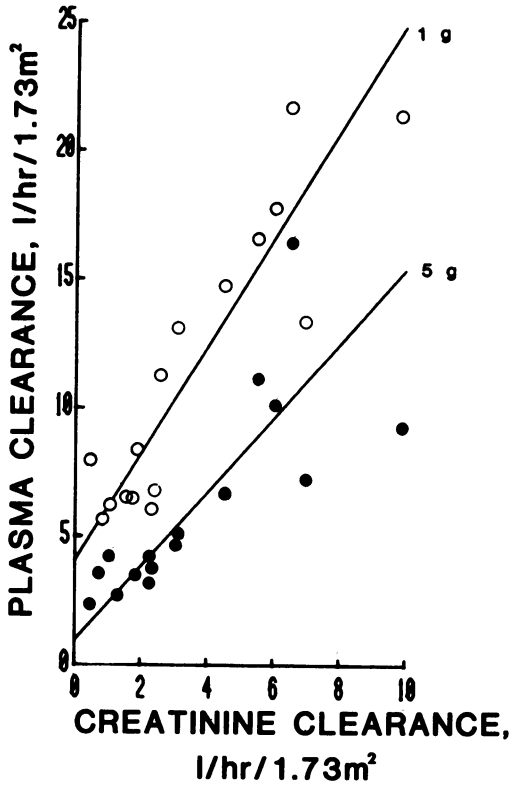

FIG. 3. Relationship between Cl_P of mezlocillin and Cl_{CR} in 16 adult subjects. These and subsequent regression lines were fitted by the weighted perpendicular least-squares method assuming error in both variables (17). Slopes (m) and intercepts (b) are: m = 2.07, b = 4.06 (1-g dose); m = 1.44, b = 0.95 (5-g dose). Both regressions are statistically significant ($P < 0.001$).

The Cl_R values of mezlocillin are shown in relation to Cl_{CR} in Fig. 4. There was a tendency towards larger Cl_R values with the 1-g dose, with a ratio of Cl_R-1 g/Cl_R-5 g averaging 1.29 ± 0.35 (t = 3.12, $P < 0.01$). Both sets of Cl_R data displayed the typical correlation with Cl_{CR}. The somewhat greater Cl_R occurring at higher plasma concentrations accounts for the lack of parallelism in the decline of plasma concentrations and excretion rates (Fig. 1 and 2). This does not allow simultaneous curve-fitting of these functions in each subject.

The total urinary recoveries of mezlocillin are shown in Fig. 5. As anticipated, renal impairment resulted in a greater fraction of the dose being eliminated by nonrenal routes. However, the percent urinary recoveries of drug were generally greater (by 1.68 ± 0.56-fold) for the 5-g dose (t = 6.22, $P < 0.001$). A specific function or regression relationship cannot be applied to these data because they reflect the multiple effects of dose and Cl_{CR}, Cl_R, and Cl_{NR} processes.

The Cl_{NR} values for mezlocillin are shown in Fig. 6 in relation to Cl_{CR}. Surprisingly, the data after the 1-g dose show a significant linear relationship. In contrast, the Cl_{NR} values after the 5-g dose did not correlate with Cl_{CR} ($P < 0.3$) and remained relatively constant at 2.71 ± 1.65 liters h^{-1} 1.73 m^{-2}, except for two relatively high Cl_{NR} values.

Distribution volumes. No relationship was found between V_c and V_{ss} of mezlocillin after 1- and 5-g doses as a function of Cl_{CR}. Mean values (± standard deviation) were: V_c = 0.127 ± 0.059 and 0.093 ± 0.036 liter per kg at 1- and 5-g doses ($P < 0.005$), and V_{ss} = 0.201 ± 0.057 and 0.138

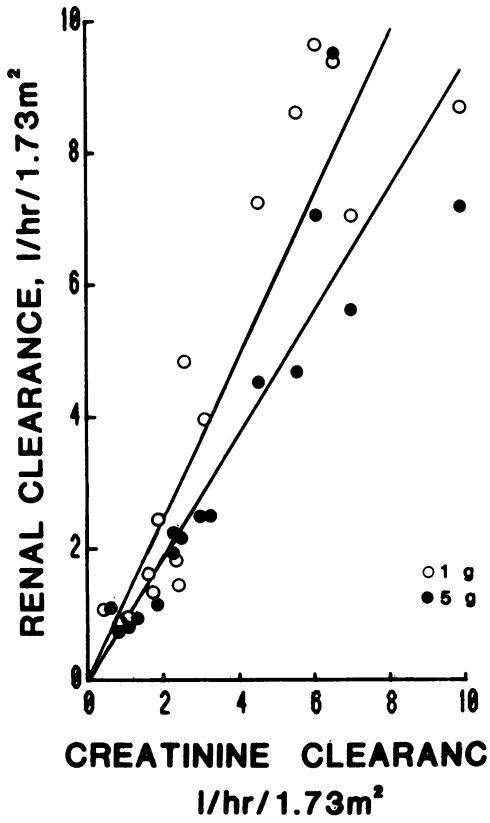

FIG. 4. Relationship between the dose-average Cl_R of mezlocillin and Cl_{CR}. The regression lines are: m = 1.25, b = 0 (1-g dose); m = 0.97, b = 0 (5-g dose) (both $P < 0.001$).

± 0.050 liter per kg at 1- and 5-g doses ($P < 0.001$). However, in spite of the general fourfold variability among subjects in V_c and V_{ss} values, there was a distinct dose dependence in each parameter. The V_c ratios even more strongly differed with dose, averaging 0.69 ± 0.17 (t = 6.87, $P < 0.001$).

DISCUSSION

Pharmacokinetics. This study interrelates two principal determinants of mezlocillin disposition in humans: dose and renal function. As noted previously, Bergan (4) found dose dependence in mezlocillin Cl_R and Cl_{NR} in healthy volunteers. Diminished Cl_R of mezlocillin in patients with renal impairment has been found in several studies (5, 9, 12, 13). Frimodt-Möller et al. (9) have examined the disposition of 2- and 4-g doses of mezlocillin in patients with various Cl_{CR} values. The doses were not crossed over in individual patients, and the variability of the data in relation to the number of subjects in poor, moderate, and normal categories of renal function diminished their ability to separate the effects of dose and Cl_{CR}. However, the tendencies of many of their parameters mimic the results of the present study. All of the previous studies reflect the strong dependence of Cl_p and Cl_R on Cl_{CR} and indicate that a variable and partial fraction of the dose is excreted unchanged in urine. They also show that V_c and V_{ss} are relatively small and indicative of the limited tissue binding of the drug, a characteristic seemingly common to the penicillins (2, 7).

Cl_R of mezlocillin (Fig. 4) exceeded the Cl_{CR} only slightly (mean ratio = 1.12). As the antibiotic is moderately (16 to 42%) bound to plasma proteins (Miles Pharmaceuticals, personal communication), an appreciable fraction of the drug in plasma must undergo active tubular secretion. This is supported by data of Verbist et al. (20), who found that probenecid reduces the Cl_R of mezlocillin by about one half. Saturation of the tubular secretory mechanism of mezlocillin is the probable explanation for the reduction in Cl_R with dose. This concentration-dependent mechanism is common to weak acids (22).

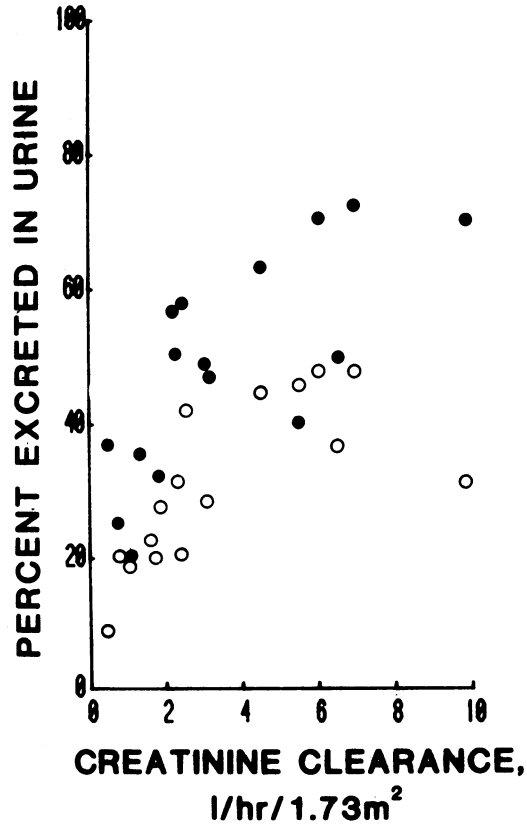

FIG. 5. Relationship between fraction of the mezlocillin dose excreted in urine and Cl_{CR} after 1- (○) and 5-g (●) doses.

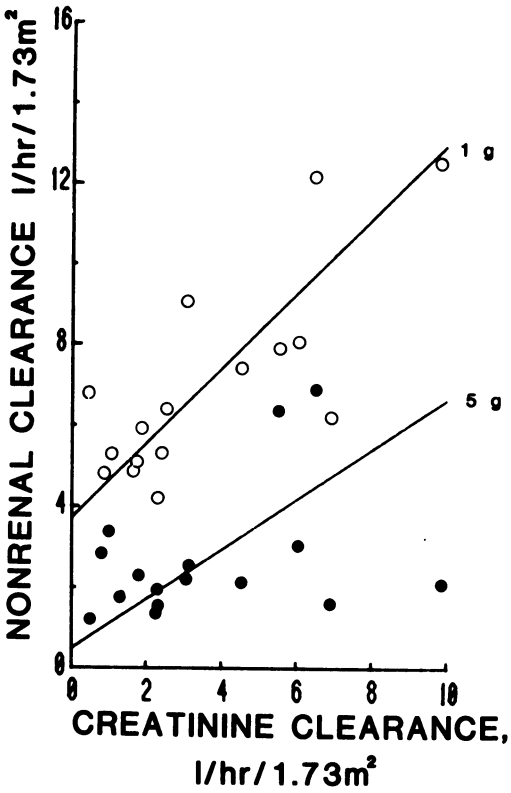

FIG. 6. Relationship between the Cl_{NR} of mezlocillin and Cl_{CR}. Regression lines are: m = 0.92, b = 3.72 (1-g dose) ($P < 0.001$); and m = 0.61, b = 0.49 (5-g dose) ($P < 0.3$).

The dual nonlinear and Cl_{CR}-dependent properties of Cl_{NR} are of considerable interest. It is unusual to find a secondary clearance mechanism so strongly correlating with renal function. An appreciable component of the Cl_{NR} appears to be biliary excretion, as Brogard et al. (6) report 3 to 30% of a dose of mezlocillin excreted in bile. An additional portion of the dose is probably degraded in serum and other body fluids (23). The biliary process may involve active transport, as Verbist and co-workers (20) found that probenecid treatment is accompanied by a 31% reduction in Cl_{NR} in human subjects. Such a transport mechanism may explain the lower Cl_{NR} values which we found at the 5-g dose of mezlocillin (Fig. 6). Similar results can be observed in the data of Kampf et al. (12), who also showed relatively constant Cl_{NR} over a wide range of Cl_{CR} values in subjects given a single dose of about 4.2 g. In both studies, the constancy of Cl_{NR} at high doses may reflect the attainment of saturation. If Michaelis-Menten saturation accounts for this Cl_{NR} pattern at the two dosage levels, then the linear relationship of Cl_{NR} to Cl_{CR} at the 1-g dose may represent a condition where renal impairment raises plasma concentrations to reduce the effective time-average Cl_{NR} and also serves as a marker for the higher and more sustained AUC profile. (This might explain the results of Verbist et al. [20] described above as well.) Alternatively, renal impairment has been found to reduce enzyme activity in peripheral body tissues, particularly Na^+/K^+ transport ATPase (14). This has been hypothesized to cause reduced tissue binding and a decreased V_{ss} of digoxin in uremic patients (11).

The decreased volumes of distribution of mezlocillin at the higher dose appear also to be unusual phenomena. A similar tendency can be noted in the data of Bergan (4), who found a mean V_c-5 g/V_c-1 g ratio of 0.74. Saturation of plasma protein-binding sites at higher plasma concentrations would have the opposite result. The V_{ss} expressed as liters per kilogram is a mean tissue-plasma partition coefficient, and a smaller value is indicative of reduced tissue uptake or binding. Gengo et al. (Abstr. Am. Pharm. Assoc. Acad. Pharm. Sci., 1980) found a marked saturation in tissue uptake of methicillin in rabbits, a phenomenon of similar nature causing a reduced V_{ss} at higher doses.

Another explanation for the change in V_{ss} with dose relates to the method of calculation. We recently found that employment of the SHAM approach, though advantageous for the reasons stated previously, may yield artifactual changes in V_{ss} with dose for drugs which also show nonlinear changes in Cl_p. Although V_c was unaffected, no alternative method exists for calculating V_{ss} after single-bolus doses of a drug. However, in the case of methicillin (Gengo et al., Abstr. Am. Pharm. Assoc. Acad. Pharm. Sci., 1980), direct tissue assays were used to confirm the SHAM analysis.

Three separate dose-dependent processes accounting for mezlocillin pharmacokinetics in humans have thus been found. However, none of the individual effects was unexpected, as penicillins and cephalosporins have demonstrated the capability for active transport in intestinal absorption (19), cerebrospinal fluid-blood transport (8), tissue uptake (Gengo et al., Abstr. Am. Pharm. Assoc. Acad. Pharm. Sci., 1980), renal tubular secretion (2, 7), and reabsorption (1).

Clinical implications. The primary pharmacokinetic determinant of therapeutic dosage regimens is Cl_p. The strongly linear dependence of Cl_p on Cl_{CR} with the limited variability in the data (at least in patients without hepatic dysfunction) is indicative of the probable ease in adjusting drug dosage regimens in patients with renal dysfunction. The dose dependence, although it complicates dosage regimen predictions, may also enhance therapy, as the nonpro-

TABLE 2. Intervals for 5-g/70 kg doses of mezlocillin

Cl_{CR} (liters h^{-1} 1.73 m^{-2})	Cl_{CR} (ml/min)	τ
0.5	<10	48
1	11–25	36
2	26–40	24
4	41–80	12
6	81–120	10
8	>120	6

portional increase in AUC with dose provides extra drug for bactericidal effects. The latter is advantageous only for drugs, such as mezlocillin, which possess a relatively large therapeutic index with a low incidence of adverse effects (16).

Rationalization of therapy can be accomplished by adjusting drug doses in patients with renal impairment to provide equivalent maximum plasma concentrations and also similar AUC values over the total period of drug therapy. This aim necessitates the adjustment of the dosing interval (τ) rather than modification of the drug dosage. Equations to do this can be derived from the following pharmacokinetic equivalency:

$$Cl_p = \frac{D_0}{AUC} = \frac{D_0}{\bar{c} \cdot \tau} \quad (9)$$

where $\bar{c}$ is a time-average plasma concentration which, when multiplied by τ, produces a given AUC. If a standard dose of 5 g/6 h is accepted as a reasonable starting dose for patients with good renal function (Miles Pharmaceuticals, personal communication), then dosage adjustments based on 5 g given at various intervals can be sought in treating patients with renal impairment. For the 5-g dose, the Cl_p can be predicted from:

$$Cl_p = 0.95 + 1.44\, Cl_{CR} \text{ (liters } h^{-1}\, 1.73\, m^{-2}) \quad (10)$$

as seen in Fig. 3. Thus the combination of equations 9 and 10 yields the following solution for τ:

$$\tau \text{ (h)} = \frac{D_0}{\bar{c}(0.95 + 1.44\, Cl_{CR})} = \frac{58}{0.95 + 1.44\, Cl_{CR}} \quad (11)$$

where the units of Cl_{CR} are liters per hour per 1.73 m^2.

Since subjects with normal renal function who receive a 5-g dose of mezlocillin every 6 h would achieve a $\bar{c}$ of 87 mg/liter (AUC/6), their quotient of $D_0/\bar{c}$ = 58 liters h^{-1} 1.73 m^{-2}, which appears in the numerator above.

Thus equation 11 can be used to generate the intervals for giving 5-g/70 kg doses of the drug shown in Table 2. These calculations are approximate and conservative and are based both on the parameters from and the hypothesis that 5-g doses of mezlocillin are appropriate. If more frequent doses are given, it should be recognized that accumulation will occur. These preliminary guidelines evolve from pharmacokinetic principles, and larger doses may be warranted in patients with severe infections, smaller doses may be needed if hepatic dysfunction is present, and any final dosage recommendations should be based on clinical experiences with such dosages in the types of patients requiring mezlocillin therapy.

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LITERATURE CITED

1. **Arvidson, A., O. Borgå, and G. Alván.** 1979. Renal excretion of cephapirin and cephaloridine: evidence for saturable tubular reabsorption. Clin. Pharmacol. Ther. 25:870–876.
2. **Barza, M., and L. Weinstein.** 1976. Pharmacokinetics of the penicillins in man. Clin. Pharmacokin. 1:297–308.
3. **Bennett, J. V., J. L. Brodie, E. J. Benner, and W. M. M. Kirby.** 1966. Simplified accurate method for antibiotic assay of clinical specimens. Appl. Microbiol. 14:170–177.
4. **Bergan, T.** 1978. Pharmacokinetics of mezlocillin in healthy volunteers. Antimicrob. Agents Chemother. 14:801–806.
5. **Bergan, T., E. K. Brodwall, and E. Wilk-Larsen.** 1979. Mezlocillin pharmacokinetics in patients with normal and impaired renal functions. Antimicrob. Agents Chemother. 16:651–654.
6. **Brogard, J. M., J. Kopferschmitt, J. P. Arnaud, M. Dorner, and J. La-Villaureix.** 1980. Biliary elimination of mezlocillin: an experimental and clinical study. Antimicrob. Agents Chemother. 18:69–76.
7. **Dittert, L. W., W. O. Griffen, J. C. LaPiana, F. J. Shainfield, and J. T. Doluisio.** 1969. Pharmacokinetic interpretation of penicillin levels in serum and urine after intravenous administration, p. 42–48. Antimicrob. Agents Chemother. 1968.
8. **Dixon, R. L., E. S. Owens, and D. P. Rall.** 1969. Evidence of active transport of benzyl-^{14}C-penicillin from cerebrospinal fluid to blood. J. Pharm. Sci. 58:1106–1109.
9. **Frimodt-Møller, N., S. Maignard, R. D. Toothaker, R. W. Bundtzen, M. V. Brodey, W. A. Craig, P. G. Welling, and P. O. Madsen.** 1980. Mezlocillin pharmacokinetics after single intravenous doses to patients with varying degrees of renal function. Antimicrob. Agents Chemother. 17:599–607.
10. **Jusko, W. J.** 1980. Guidelines for collection and pharmacokinetic analysis of drug disposition data, p. 639–680. *In* W. E. Evans, J. J. Schentag, and W. J. Jusko (ed.), Applied pharmacokinetics. Applied Therapeutics, Inc., San Francisco.
11. **Jusko, W. J., and M. Weintraub.** 1974. Myocardial distribution of digoxin and renal function. Clin. Pharmacol. Ther. 16:449–454.
12. **Kampf, D., R. Schurig, K. Welhermüller, and D. Förster.** 1980. Effects of impaired renal function, hemodialysis,

and peritoneal dialysis on the pharmacokinetics of mezlocillin. Antimicrob. Agents Chemother. 18:81–87.

13. **Kosmidis, J., P. Doundoulaki, Ch. Stathakis, N. Zerefos, A. Bounia, and G. K. Daikos.** 1979. Elimination kinetics of mezlocillin in normal and impaired renal function including the effects of dialysis. Arzneim.-Forsch. 29:1960–1962.
14. **Kramer, H. J., A. Backer, and F. Kruck.** 1974. Inhibition of intestinal ($Na^+ - K^+$) ATPase in experimental uremia. Clin. Chim. Acta 50:13–18.
15. **Metzler, C. M., G. L. Elfring, and A. J. McEwen.** 1974. A package of computer programs for pharmacokinetic modeling. Biometrics 30:562.
16. **Pancoast, S., J. Jahre, and H. C. Neu.** 1979. Mezlocillin in the therapy of serious infections. Am. J. Med. 67:747–752.
17. **Riggs, D. S., J. A. Guarnieri, and S. Addelman.** 1978. Fitting straight lines when both variables are subject to error. Life Sci. 22:1305–1360.
18. **Snedecor, G. W., and W. G. Cochran.** 1967. Statistical methods, p. 91–101, 6th ed. Iowa State University Press, Ames.
19. **Tsumi, A., E. Nakashima, I. Kagami, T. Asano, and R. Yamana.** 1978. Kinetics of Michaelis-Menten absorption of amino-penicillins in rats. J. Pharm. Pharmacol. 30:508–509.
20. **Verbist, L., T. B. Tjandramaga, R. Verbesselt, and P. J. DeSchepper.** 1979. Mezlocillin pharmacokinetics. Comparison with ampicillin and influence of probenecid. Arzneim.-Forsch. 29:1962–1966.
21. **Wagner, J. G.** 1976. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J. Pharmacokin. Biopharm. 4:443–467.
22. **Weiner, I. M.** 1971. Excretion of drugs by the kidney, p. 328–353. *In* B. B. Brodie, J. R. Gillette, and H. S. Ackerman (ed.), Handbook of experimental pharmacology. Springer-Verlag, Heidelberg.
23. **Wise, R.** 1979. Azlocillin and mezlocillin, two new alpha-amino substituted penicillins. Arzneim.-Forsch. 29:1929–1932.